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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/608,997	06/27/2003	Darwin J. Prockop	053844-5002-01US	8493
28977	7590	12/16/2005	EXAMINER	
MORGAN, LEWIS & BOCKIUS LLP 1701 MARKET STREET PHILADELPHIA, PA 19103-2921			KELLY, ROBERT M	
			ART UNIT	PAPER NUMBER
			1633	
DATE MAILED: 12/16/2005				

Please find below and/or attached an Office communication concerning this application or proceeding.

<p align="center"><b>Office Action Summary</b></p>	<p>Application No.</p> <p align="center">10/608,997</p>	<p>Applicant(s)</p> <p align="center">PROCKOP ET AL.</p>	
	<p>Examiner</p> <p align="center">Robert M. Kelly</p>	<p>Art Unit</p> <p align="center">1633</p>	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 26 October 2005.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) 9-15 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-8 and 16-18 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 27 June 2003 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| <p>1) <input type="checkbox"/> Notice of References Cited (PTO-892)</p> <p>2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)</p> <p>3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br/> Paper No(s)/Mail Date _____.</p> | <p>4) <input type="checkbox"/> Interview Summary (PTO-413)<br/> Paper No(s)/Mail Date. _____.</p> <p>5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)</p> <p>6) <input type="checkbox"/> Other: _____.</p> |
|--|---|

### **DETAILED ACTION**

Applicant's amendments and arguments of 10/26/05 are entered.

Claim 1 is amended.

Claims 1-18 are pending.

### ***Election/Restrictions***

Applicant's election without traverse of Group I, claims 1-8 and 16-18, drawn to a method of directing the differentiation of an isolated stromal cell into a neural cell in a human patient suffering from a disease, disorder, or condition of the central nervous system, in the reply filed on 3/25/05 was acknowledged in the Official Action of 6/3/05, pp. 2-3.

Claims 9-15 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/25/05.

This application contains claims 9-15 drawn to an invention nonelected with traverse in reply filed 3/25/05. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Furthermore, claim 17 also encompasses non-elected subject matter, as one of the species includes introducing a nucleic acid into the cells. A complete reply to the final rejection must include cancellation of the nonelected subject matter of this claim or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

### ***Claim Objections***

Claim 17 is objected to because of the following informalities: Claim 17 comprises non-elected subject matter. Appropriate correction is required.

### ***Note: Change in Art Unit and SPE***

The Examiner has been reassigned to Art Unit 1633. Therefore, future correspondence should reflect such changes. Also, at the end of the Action is the information regarding the SPE of the Art Unit.

### ***Drawings***

The drawings remains objected to under 37 CFR 1.83(a) because they fail to show, for figure 6, which sections are at 4, 14, 30, or 72 days, as described in the specification (p. 8, paragraph 2). Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as “amended.” If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either “Replacement Sheet” or “New Sheet” pursuant to 37 CFR

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1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

***Response to Argument – Drawings***

Applicant argues that figure 6 is a composite of brain sections obtained at days 4, 14, 30, or 72, and as such, being a combining of typical/essential characteristics, it is clear that Figure 6 is adequately described, and no labeling is required for specific days (Applicant's argument of 10/26/05, pp. 6-7).

Such is not persuasive. The Examiner fails to understand how these were combined. If all the brains were combined to show migration, there should logically exist only a single drawing, i.e., a section of brain, showing everywhere the various cells had been over the time frames analyzed. If however, only the brains assessed on the same day were analyzed, there should exist 4 brain sections, one for each day analyzed (it is noted that 5 might actually exist if Applicant had a control for day 0). However, Applicant's figure has six sections. Perhaps these represent the level of the brain which were sectioned, and the brain sections represent all the cells found at each time period for each animal; however, the Examiner is not the inventor and simply does not understand.

Therefore, the objection remains until Applicant clears up the matter at hand.

***Priority***

In light of Applicant's now-established priority chain, all objections to Applicant's priority are withdrawn.

***Claim Rejections - 35 USC § 112 – New Matter***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In light of Applicant's amendments to claim 1, the rejections of Claims 1-8 and 16-18 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, are withdrawn.

Specifically, while Applicant's arguments themselves are not persuasive, as Applicant has provided specific definition for what is meant by "directing the differentiation", and as such, it takes priority over any art-recognized definitions, Applicant has amended the claims to encompass "differentiating". Therefore, the rejections are withdrawn.

***Claim Rejections - 35 USC § 112 - Enablement***

Claims 1-8 and 16-18 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

***Response to Argument - Enablement***

Applicant's arguments of 10/26/05 have been fully considered but are not found persuasive.

Applicant argues, through three separate references (Kopen, et al. (1999) Proc. Natl. Acad. Sci., USA, 96: 10711-16; Hofstetter, et al. (2002) Proc. Natl. Acad. Sci., USA., 99: 2199-204; and Chopp, et al. (2000) Neuro Report, 11: 3001-05), which each appear to demonstrate

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particular therapeutic embodiments by the administration of MSCs to the CNS, and that, therefore, Applicant's claims are enabled (Applicant's argument of 10/26/05, pp. 11-14)

Such is not persuasive. First Kopen is essentially the disclosure of the present application, demonstrating that neonatal mice (which do not have a fully developed Blood-Brain Barrier), can have the cells cross from the circulatory system into the Brain, and some of these cells develop markers of various types of cells. However, Kopen does not demonstrate anything like therapy, as is explicitly evidenced by Kopen at the end of the ABSTRACT: "These results suggest that MSCs are potentially useful as vectors for treating a variety of central nervous system disorders." (ABSTRACT, *emphasis added*). As such, it is clear that Kopen even recognizes that the results are not yet reasonably predictive of any particular level of therapy for any particular disease/disorder/condition in any particular animal. With regard to Hoffstetter, the reference further buttresses that the differentiation of the MSC in the neuronal tissue may not even have a therapeutic effect (pp. 2203-04, paragraph bridging), and hence, Hoffstetter does nothing to provide any enablement. Moreover, Hoffstetter required administration to the neuronal tissue if it was administered immediately after injury, but could be infused if administered after one week (p. 2203), and moreover, none of these provide enablement for the wide range of administrations encompassed for reasons of record. Given the specific nature of administration, it appears that Applicant's specification is not even enabled for the specific treatment encountered here. With regard to Chopp, the experiments are similar to Hoffstetter, except Chopp does not report any form of administration except direct administration, and hence, given the breadth of administrations, it is still not reasonably predictable for any administration. Further none of these demonstrate differentiation into neuronal cells, and further buttresses that

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the differentiation of the MSC into a neuronal cell type may not have any therapeutic effect. Moreover, none of these experiments demonstrate treatment itself, but merely amelioration of some of the symptoms, none of the experiments teach treatment of any larger animal, and none of the experiments relate to other types of disorders, e.g., cerebral palsy, as was addressed in the Official Action of 6/3/05. Hence, these post-filing references do little to enable Applicant's claimed methods. Even if they did enable a specific embodiment, given the breadth of treatments, disorders, administrations, differentiations, etc., that Applicant's claims embrace, Applicant would at best face a narrow scope of enablement.

Applicant argues that the method is analogous to treatment of Parkinson's disease, and that animal models for these diseases were in rats, and that therefore, Applicant's claims are enabled (Applicant's argument of 10/26/05, p. 14, paragraphs 4-5). Similar arguments are made for treatment of stroke and spinal cord injury (Applicant's argument of 10/26/05, p. 15, paragraphs 1-3).

Such is not persuasive. The Artisan recognized it was not reasonably predictable, and further questioned whether disorders in small animals could translate to larger animals. The history of treating Parkinson's disease with fetal tissues, which are not MSCs, is not at issue, firstly, because the Artisan would still have to find an animal model, test it, translate it to other animal models, and then determine that Parkinson's disease could be treated with Applicant's MSCs, because the Artisan could not reasonably predict it would work in the first place. Secondly, Applicant does not just claim Parkinson's disease, but any neuronal disease, disorder or condition, which is much broader than Parkinson's disease, and hence, all of this would be required to be practiced with many other diseases before such claims would be enabled. Finally,



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Applicant's disclosure simply demonstrates that a few cells possess a marker of development into a single nervous tissue-like cell, due to the presence of a single marker: glial fibrillary acidic protein, when cultured *in vitro* with astrocytes (EXAMPLE 8), as well as the presence of such cells when directly injected into the brain of mice over a long period of time (EXAMPLE 7).

Similar arguments are made against the use of other models in treatment of other diseases. To wit, the Artisan could not predict treatment, or any treatment, and as such would have to experiment with these models, as well as a sufficient number of other models, in order to determine if any particular embodiment would be efficacious. As such, this is undue experimentation and therefore Applicant's claimed are not enabled.

Such examples simply do not correlate, given the various Wands factors analysis provided, to the claimed invention, and moreover to the breadth of the invention claimed. The Examiner fails to understand how the presence of this marker, produced *in vitro*, correlates to differentiation into so many cell types *in vivo*, in the correct proportions every time, to treat the various diseases. As has been repeatedly shown, such differentiation is not predictable, and may not even be the cause of any treatment. Therefore, the rejection is maintained for reasons of record.

### ***Conclusion***

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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